REMARKS

Claims 1-6 are pending.

Claims 1-6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Baert et al. (US 6,365,188) in view of Nagafuzi et al. (US 5,290,569). Applicants respectfully traverse this rejection.

Baert et al. describes a process for preparing a solid mixture of an active ingredient in a cyclodextrine, which process comprises a melt-extrusion step, where (a) the active ingredient is mixed with a cyclodextrine, (b) optionally additives are added, (c) the mixture is heated until one of the components melts, (d) the mixture is forced through a nozzle, and (e) the mixture is cooled until it solidifies (column 4, lines 14-23). the cooled strands are subsequently milled or pelletized. As optional additives, Baert et al. mentions e.g. plasticizers, such as polyethylene glycol (PEG) (column 4, lines 34-42). A PEG that is suitable to be used as a plasticizer is constitutionally not the same as a PEG used as a binder, the difference being essentially the distinctly higher molecular weight of the latter. This can also be seen from Klimesch et al. (US 4,880,585), where PEG on the one hand is used as a polymeric binder (see column 2, line 40 to column 3, line 1) and on the other hand as a plasticizer (column 3, lines 1-9). It would not have made any sense to name PEG both as a binder and as a plasticizer if the PEG was the same in both cases. It is well known in the art that PEGs suitable as binders have certain properties, especially a minimum molecular weight, which are distinct from the properties of PEGs useful as plasticizers. Consequently, it is clear that

Baert et al. does not teach producing solid mixtures comprising also binder.

Moreover, Baert et al. even teaches away from incorporating any further component into the solid mixture. In column 6, lines 19-22 it is said that melt-extruded mixtures are preferred which consist essentially of a solid solution of an active ingredient and a cyclodextrine, i.e. which essentially contain no further additives (see also column 4, lines 41-42).

As can be seen from the dissolution examples, especially from dissolution example 3, the products obtained by the Baert et al. process show an accelerated dissolution in artificial gastric juice.

In contrast thereto, Nagafuzi et al. describes a process for preparing a coated pharmaceutical composition characterized by a delayed release of the active substance. The process comprises the step of granulating a mixture of an active ingredient and a thermomelting material as a binder under heat without using any solvent. The weight ratio of the binder to the active ingredient is 0.05 to 0.4 parts by weight of binder to 1 part by weight of active ingredient (see column 3, lines 36-38).

A person skilled in the art would not have been motivated to incorporate the binder of Nagafuzi et al. into the process of Baert et al. Baert et al. teaches in column 4, lines 52-58 that mixing two or more solids, i.e. a cyclodextrine and an active ingredient, and subsequently melting these solids together will give rise to different products than when the said solids are first brought in to contact with water or another solvent and then extruded. From this passage, the skilled person would consequently

have deduced that mixing the active ingredient and a cyclodextrine in the presence of a binder, which can be understood as a sort of diluent, would also lead to products having different characteristics when compared to products obtained in the absence of a binder. The skilled person would have assumed that the binder can (partly) prevent the formation of a cyclodextrine/active ingredient complex --which is important for the release time, as shown by the examples of Baert et al.-- and thus leads to a slower release of the active ingredient. This assumption is supported by Nagafuzi et al., where in example 1, a preformed cyclodextrine/active ingredient inclusion complex is granulated in the presence of a binder. The obtained product shows a sustained release (see test example 3), although a preformed cyclodextrine complex is used, which normally shows a fast dissolution profile. Thus result would have led the skilled artisan to the conclusion that incorporating a binder into the composition of Baert et al. would lead to products with a slower release of the active ingredient.

The object of the present invention, however, was to provide a solid dosage from with a reduced release time. This is achieved by a dosage form obtained by the claimed process as shown by the examples and comparative examples of the present specification. Indeed, the unexpectedly quick release times of the dosage forms obtained by the claimed process evidence the nonobviousness of the present invention.

In summary, a skilled person would have had to take the following steps to arrive at the present invention:

- incorporating the binder of Nagafuzi et al. into the process of Baert et al.

- although Baert et al. teaches that it is preferred not to incorporate any further substances, and
- although the Nagafuzi et al. combination comprising the active ingredient, the cyclodextrine and the binder leads to an effect opposite to the desired fast release; and

- choosing a weight ratio of binder and active substance outside the range of Nagafuzi et al.'s composition (Nagafuzi et al.: 0.05-0.4:1; present invention: 0.6-196:1).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. MPEP 2143.01. Since the two cited references give no incentive to make the aforementioned modifications, but actually teach away from doing so, the claimed process would not have been obvious over Baert et al. in view of Nagafuzi et al.

Claims 1-6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mueller et al. (US 5,552,159) in view of Baert et al. (US 6,365,188). Applicants respectfully traverse this rejection.

Mueller et al. teaches a process for preparing solid depot drug forms by melt-extrusion at from 50 to 200°C and continuous shaping of a mixture of from 0.1 to 70% by weight, based on the finished depot form of a pharmaceutically active ingredient with a polymer melt comprising at least 6% by weight of a water-insoluble poly(meth)-acrylate and a water-soluble polymer selected from hydroxyalkylcellulose,

hydroalkylmethylcellulose and an N-vinylpyrrolidone homo- or copolymer with vinylacetate. The thus obtained drug forms show a delayed release of the active ingredient (see column 2, lines 13-16).

The same arguments pertaining to the above rejection apply here as well. A skilled person would not have been motivated to incorporate into the composition of Baert et al. the polymeric binder of Mueller et al. since he would have expected a delayed release of the active ingredient instead of the desired accelerated release. The skilled person would also have had no incentive to incorporate the cyclodextrine of Baert et al. into the composition of Mueller et al. because he would have considered that the beneficial effect of the cyclodextrine/active ingredient composition of Baert et al. would have been completely annihilated by the combination with a binder. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP 2143.02.

Claims 1-6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Meerpoel et al. (WO 99/58529) in view of Klimesch et al. (US 4,880,585). Applicants respectfully traverse this rejection.

Meerpoel et al. describes solid dosage forms for parenteral applications which can be obtained in a melt-extrusion process comprising the steps of (a) mixing an active compound and a water-soluble polymer, (b) optionally blending additives with this mixture, (c) heating the thus obtained blend until the formation of a homogeneous melt,

(d) forcing the melt through a nozzle, and (e) cooling the melt until it solidifies (p. 27, lines 20-28). Suitable water-soluble polymers are said to be, among others, polyvinylpyrrolidone, vinylpyrrolidone/vinyl acetate copolymer, polyalkylenoxide, etc. (p. 27, line 33 to p. 28, line 5). As alternative water-soluble polymers are named cyclodextrines (p. 28, lines 7-11). The combination of active ingredient, one of the first mentioned polymers and cyclodextrine is not mentioned.

Klimesch et al. describes a process for preparing a solid dosage form, the process comprising extruding a mixture and pressing the still deformable extrudate between two rollers which are driven in opposite directions and possess depressions opposite one another in the roller shell. Extrudable pharmaceutical mixtures are said to be mixtures of pharmaceutically active compounds with auxiliaries conventionally used for the preparation of pharmaceutical tablets, such as binders, e.g. polyvinylpyrrolidone, copolymers of N-vinylpyrrolidone and vinyl acetate, polyethyleneglycol and the like.

A combination of these two references does not lead to the claimed invention because Meerpoel et al. does not teach using a mixture of an active ingredient, a cyclodextrine and a binder. The cyclodextrine in Meerpoel et al. is only mentioned as an alternative water-soluble polymer, and not as an additional component in the mixture. Moreover, Meerpoel et al. does not mention the role of cyclodextrines as solubilizers and especially not their impact on the release time of the active ingredient from the solid dosage form. Therefore, a skilled person would not have found the slightest suggestion to use a cyclodextrine in additional to the other polymeric binders

enumerated in Meerpoel et al.

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Respectfully submitted,
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